

Targeting Autophagic Pathway in Oral Cancer Therapy Through Phytoconstituents: A Short Review

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Oral cancer was recognized as the most common type of cancer in South Asian countries including India. As concurrent chemoradiotherapy leads to various associated new problems, there is always a need for improved therapies without side effects. Natural plant products used since ancient times may fill the gap. Phytoconstituents can activate various cell death pathways, such as apoptosis, autophagy, or pyroptosis to treat oral tumors. Numerous studies have already been done to date to enlighten the detailed mechanism of the use of phytoconstituents in these cell-signaling pathways. As the majority of the studies emphasized the apoptotic pathway, the least reports are found on autophagy. 'AMPK' and 'mTOR' have been acknowledged to be the key signaling compounds that modulate autophagy. Therefore the objective of this article is to discuss the mechanism of autophagy concerning phytoconstituents in the treatment of oral carcinoma.

Keywords: AMPK; Autophagy; mTOR; Oral cancer; Phytoconstituents.

The mechanism of autophagy is a cellular recycling process that attempts to maintain the removal of unwanted proteins as well as unhealthy or old organelles¹. The molecular mechanics of the process of autophagy through various types of actions are least specified². There are several chemotherapy-resistant mechanisms available which include cell death processes like autophagy and apoptosis, multi-drug resistance, cancer cell heterogeneity, and cancer micro-environment pressure-induced genetic or epigenetic modifications. Along with the above factors, alterations in two self-disparaging procedures (apoptosis and autophagy) might

initiate better therapies^{3,4} for cancer treatment. Phytochemicals trigger different cell death pathways, such as apoptosis, autophagy, or pyroptosis.

Numerous studies have already been performed to date to explain the detailed mechanism of the use of phytochemicals in these cell-signaling pathways. The potential purpose of phytochemicals during the process of apoptosis, as well as autophagy, was analyzed elaborately by Deng⁵ and his co-workers, in 2019. As most studies emphasized the apoptotic pathway, the least reports are found on autophagy. So, this study attempts to summarize the use of phytochemicals in various autophagy pathways treating oral cancer.

Autophagy in carcinoma pathway

Autophagy conserves as a lively interconnection in cell protection and a cytostatic association in carcinoma cell development⁶. The procedure introduced by the production of phagophore assemblage sites (PAS)⁶, Phosphatidylinositol 3-phosphate (PI3K) along with the endoplasmic reticulum/ER, was found to have a crucial function in the configuration of PAS⁷. Adenosine Monophosphate activated protein kinase (AMPK), mammalian target of rapamycin shortly termed 'mTOR' and unc-51 autophagy activating kinase-1 (ULK1) found making easy phagophore development through autophagy initiation⁸, by the help of Vps15/p150, Vps34 and Beclin-1 in phagophore configuration⁹. The formation of phagophores, results in phagocytosis, consequently ending in elongation and sealing the membrane meant for the formation of autophagosome¹⁰. Adult autophagosomes attach with lysosomes, resulting in the development of autolysosomes². Thus autolysosomes can be demolished by acidic hydrolases, help in additional recycling metabolism and consequently conserve cellular equilibrium.

However, mTOR is very significant in autophagy by defending or activating oncogenic cells. Chemotherapy drugs hold back cancer cells by altering the pathway of autophagy. So autophagy can be termed either a cellular existence or demise system¹¹ and displays a vital position in maintaining metabolic adjustment in cancerous cells¹². AMPK and mTOR have been recognized to be the most important signaling molecules that enhance autophagy through amino acids and the level of glucose⁸. Anyways, specified metabolites like palmitate, oxygen concentration, ATP to ADP ratio, particular levels of certain amino acids, ROS, growth factors as well as oncogenes control autophagy instigation and autophagosome construction. It has been confirmed by Youn¹³, that genes like Phosphatase and Tensin homolog deleted on chromosome 10 (PTEN), Beclin-1, and Death associated protein kinase 1 (DAPK 1) are cancer-suppressing and regulate the autophagy pathway. The expressed PTEN may endorse downregulation of the PI3K/AKT pathway, disturbing cancer augmentation by invigorating autophagy.

Development of autophagy in oral carcinoma

Autophagy is an actively impartial cellular

process where unwanted nonfunctional cellular molecules break down or disintegrate by synthesis with lysosomes⁶; This cellular procedure plays a key role in regulating cell function and homeostasis. So autophagy conserves a dynamic relation in cell protection mechanism and a cytostatic linkage in tumor cell development⁶.

Autophagy-related genes like ATG7 take part in the covalent bonding between ATG5 - ATG12 in the membrane of autophagosome as an E1-like ubiquitination activase. Except, ATG8, recognized as microtubule-associated protein 1 light chain 3 (MAP1LC3 or LC3), is decisive for autophagy. Autophagy having dual activity can either enhance or restrict the onset of tumorigenesis. According to Saha¹⁴, autophagy may enhance the growth of tumor cells supplying nutrients in the later stage, still in the early stage, a long non-coding RNA FLJ22447 restricts autophagy of the cancer-associated fibroblasts (CAFs) and regulates the autophagic filth of IL33, where CAFs produce sufficient IL33 for the propagation of OSCC cells. Researchers like Zhang¹⁵ established that the neutrophil gelatinase-associated calcitonin (NGAL) gene activates mTOR, by blocking autophagy and enhancing OSCC. The mTOR protein kinase is a key downbeat controller of autophagy¹⁶ and controls numerous cell signaling pathways affecting cell growth, most of which with tyrosine kinase activity exhibit downstream growth factors. Structural activation of RAS, PI3K, AKT (activation mutation) and PTEN (inactivation mutations) are regularly found in cancer development. So Poillet-Perez and White¹⁷ suggested autophagy inhibition may endorse tumor intensification.

Then autophagy-mediated Oral carcinoma can be distinguished as ROS-dependent NUPR1-mediated autophagy, microRNA-mediated autophagy, or long Non-coding RNA-mediated autophagy. Autophagy in oral carcinoma treatment was established by various researchers in different ways. Some established CerS6 to enhance cisplatin-associated chemotherapy¹⁸, some regulated the ATG gene to block the oral carcinoma development and some tried to modify autophagy-related noncoding RNA to prevent oral carcinoma¹⁹.

Phytochemicals involved in cancer through autophagy

The Table. 1 gives a brief idea about some

Table 1. Some popular plant derivatives used in cancer therapy through autophagy

S. No.	Name of the phyto chemicals	Plant source	Cancer type	Signaling pathway	References
1	Gintonin (Glycoprotein)	<i>Panax ginseng</i>	Central Nervous System	Akt/mTOR/p70S6K-mediated pathway	20
2	Allicin (sulphur compound)	<i>Allium sativum</i>	Lung cancer	A549 cells by ROS accumulation and facilitating S/G2-M phase arrest	21
3	Curcumin (polyphenolic compound)	<i>Curcuma longa L.</i>	Multiple cancers	PI3K/mTOR signaling pathway Autophagy in NSLCA549 cells	22 23
4	Apigenin (Flavonoid)	<i>Justicia gendarussa</i>	Hepatocellular carcinoma	Increased ROS and DNA damage, phosphorylation of ERK1/2 and p38 AMPK, inhibited Akt and P54 JNK	24
5	Aspalathin (polyphenolic compound)	<i>Aspalathus linearis</i>	Prostate cancer	PI3K/Akt/mTOR pathway	25
6	Hispolon (Polyphenol)	<i>Phellinus igniarius (L.)</i>	Naso-pharyngeal cancer	Kinase pathway/cell cycle at G2/M phase	26
7	Toxicaricoid O	<i>Aniracaria</i>	Colon, Pancreas, Ovarian And breast cancer	AMPK and Fox pathways	27
8	Berberine (Alkaloid)	turmeric, Oregon grape, goldenseal, and European barberry.	Prostate cancer	ERK pathway	28
9	Celastrol (tri terpenoid)	<i>Tripterygium wilfordii</i>	Prostate cancer	Akt/mTOR pathway	29
10	Evodiamine (quinolone alkaloid)	<i>Evodia rutaeacarpa</i>	Multiple cancer	AMPK/mTOR/ULK1 pathway	30
11	Fisetin (flavonoid)	Strawberries, apples, persimmons, onions and cucumber	Prostate cancer	AR signaling pathway	31
12	Genistein (Isoflavon)	legumes,	Ovarian cancer	Beclin-1 and Bax expression for upregulation and Bcl-2 downregulation TOR signaling pathway	32 33
				Aktphosphorylation	34

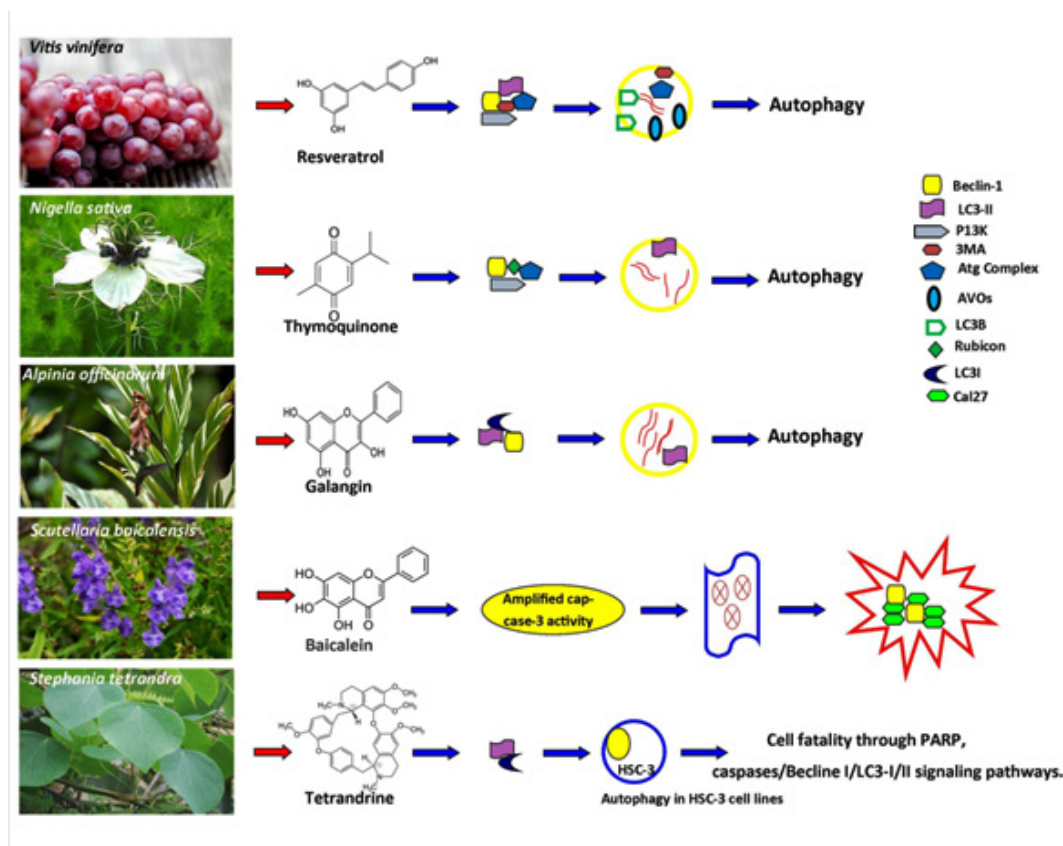


Fig. 1. Depicts the different phytochemicals involved in autophagy through different pathways in oral cancer

popular plant derivatives used in cancer therapy through autophagy.

Phytochemicals affecting oral cancer therapy through autophagy

F.S. Yu³⁵ reported on the cytotoxicity of tetrandrine over HSC-3 human oral cancer cells through autophagy and apoptosis. Tetrandrine improved LC3-I and -II expression initiating autophagy in HSC-3 cell lines. So tetrandrine-mediated autophagy in HSC-3 cells leads to cell fatality through PARP, caspases(3,8,9)/Beclin I/LC3-I/II signaling pathways. The autophagy induced by tetrandrine through the Wnt/ β -catenin pathway was also established by Zhang³⁶. Chang³⁷ for the first time revealed the resveratrol-mediated cell autophagy as well as apoptosis in cisplatin-resistant human oral tumor cells. They suggested resveratrol initiated autophagy vesicle formation, AVOs, and LC3B(Auto phagosome formation) in CAR cells. This also affects mRNA expression of genes like Beclin-1, LC3-II, Atg5, and Atg12,

and is responsible for autophagy in CAR cells. This improves autophagy-involved proteins like Beclin-1, LC3-II, PI3K class III, 3-MA (an inhibitor of PI3K class III), and Atg complexes repressed the autophagic vesicle configuration by resveratrol. Chu³⁸ demonstrated the action of thymoquinone(TQ) against 4 types of oral carcinoma cell lines (SAS, SCC-4, OC2, and SASVO3) of which SASVO3 cells were found to be mostly affected. Expression of autophagy-related proteins like Beclin-1, Rubicon, Class III, PI3K family, and Atg complex proteins, initiated autophagy by the formation of the autophagosome. Then LC3-I is attached to the lipid phosphatidyl ethanolamine and LC3-II is produced which is, an indicator of autophagy. mTOR is concerned with TQ-induced autophagy. Galangin stimulated autophagy by overexpressed genes like LC3I, LC3II, and Beclin 1 was demonstrated by Wang³⁹, which ended that galangin may cause human laryngeal carcinoma cell death, contributing to

tumor suppression. Autophagy initiation was identified by Beclin-1 enhancement and p62 degradation which concluded that baicalein treatment induced autophagy in the OSCC cells. According to Li⁴⁰, baicalein outstandingly amplified caspase-3 activity after repressing autophagic flux. This disclosed that baicalein-initiated autophagy reticence enhanced Cal27 cells to baicalein-initiated cell fatality by apoptosis. The autophagic pathways of the above-mentioned phytoconstituents are represented in Figure 1.

CONCLUSIONS AND FUTURE PERSPECTIVES

Autophagy is an extremely multifaceted metabolic procedure that performs a decisive position in the body's resistance to diseases. It shows a bifurcated effect over oral cancer. The outcome of autophagy on the incidence and expansion of oral cancer is mostly by the expression of autophagy-related genes. Plants and their bioactive products, which are rewards from mother nature to the human race, showed considerable anticancer activity and possess the capability to hold back the initiation and expansion of oral cancer, adopting mostly the apoptotic pathway. Phytochemicals in the pathway of apoptosis are widely studied in cancer therapeutics especially oral carcinoma, whereas the study of autophagy is almost neglected. That's why there is a need for exploration of autophagic mechanisms and an explanation of the connection between the signaling pathway of autophagy and oral cancer. So we tried to put an insight into the process of autophagy in OSCC by the phytoconstituents which may help the researchers in the development of novel drugs.

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Conflict of Interests

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Data availability

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Author contributions

SS performed literature searches and wrote the manuscript. SKB reviewed the manuscript. RB edited and designed the manuscript. All authors contributed to manuscript revision, and approved the submitted version.

Ethical approval

Not applicable.

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